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A STUDY OF ADDISON'S DISEASE AND OF THE ADRENALS.[1]

BY W. GILMAN THOMPSON, M.D.,
OF NEW YORK.

SINCE the description was published by Addison, in 1855, of the disease which bears his name, much study has been expended upon the etiology of this remarkable affection. The present research has been undertaken with the view of formulating such conclusions in regard to the etiology and symptomatology of Addison's disease as our still limited knowledge of the subject justifies. My personal experience includes three cases with autopsies, and to these are added three more, which are all that careful search discovered among the statistics for the past ten years of the New York and Presbyterian Hospitals. In addition, I have collected unreported records of 40 autopsies in which lesions of the adrenals have been noted, but without accompanying symptoms of Addison's disease.

In two exhaustive articles by Lewin (*Charité Annalen*, 1885, p. 630; 1892, p. 536), all cases of Addison's disease and of diseases of the adrenals which were reported prior to the latter part of 1891 were tabulated, to the number of 684. I have brought this work up to date, analyzing 73 more histories. This total of 757 cases recorded by many different observers constitutes a series large enough to afford definite data, since autopsies were made in nearly all.

The term "Addison's disease" strictly applies to an affection which, as described by Addison himself (*Dr. Addison's Works*, New Sydenham

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[1] Read before the Association of American Physicians at Washington, May 30, 1893.

Soc., 1868, p. 211), includes, among less characteristic features, extensive bronzing of the skin; but since in many instances the pigmentation is absent, while the other symptoms are decided, and are accompanied by the lesions common to the typical form, conclusions will be drawn from both classes.

The six new cases are here annexed. All were characterized by very decided bronzing of the surface of the entire body, which in one instance only was accentuated here and there by oval spots of a blacker hue. In addition, all the patients presented a group of definite symptoms, viz., great muscular weakness and prostration, indistinct heart-sounds, feeble pulse, pronounced gastric irritation with repeated attacks of nausea and of almost uncontrollable vomiting, mental apathy, and local pain.

In three of the cases in which autopsies were obtained, both adrenals were found softened and degenerated to a degree which entirely obliterated their original structure.

The first of the cases which came under my care was so unusual that it deserves special mention.

CASES OF ADDISON'S DISEASE PREVIOUSLY UNREPORTED.

CASE I.—The patient, J. A., was an intelligent Irishman, fifty years of age. He was admitted to the Presbyterian Hospital on May 5, 1891. He contracted syphilis several years before, and also suffered from frequent severe attacks of malarial fever during a three years' residence in Central America. Eight months before admission he noticed discoloration of the skin, general muscular weakness, and indigestion, especially of fatty food. He also had more or less diarrhœa, and for two months he suffered greatly from nausea and vomiting. On three occasions he was seized with sudden faintness, accompanied by severe pain in the right hypochondriac region. Five months before admission his skin began to darken and became more and more bronzed. The color appeared first upon the face and later upon the trunk and extremities. The intensity of the discoloration varied from time to time, but on the whole progressed quite rapidly.

On admission the chief complaint was of general muscular weakness. Physical examination of the lungs and abdominal viscera revealed nothing abnormal. Heart-sounds extremely feeble, pulse feeble, soft, compressible, 72. Respiration and temperature normal. Urine normal. Red blood-cells 1,922,000 per cubic millimetre. Body ill-nourished, but not emaciated. The face and hands were of a dull mahogany-brown color, the rest of the integument of a lighter brown.

After several days of rest and tonic treatment the patient gained in strength and was allowed to go out for exercise. After some hours he returned very hungry, and said that he had been evicted from three restaurants where he applied for lunch, on the ground that he appeared to be a negro, which indeed he resembled. After this experience he remained in the hospital, and became progressively weaker and mentally dull, with a rapid and extremely feeble pulse. He also had another seizure of pain in the right hypochondrium, which was very intense and followed an evacuation of the bowels. The visible mucous membranes became pigmented.

The man suddenly developed pneumonia and died on the thirteenth day.

The *autopsy* showed both the adrenals to be normal. The liver exhibited syphilitic cirrhosis. The splenic capsule was thickened and adherent, and the spleen itself was soft. There was some thickening of the duodenal mucous membrane. Pneumonia was present at the base of the right lung. Nothing else of importance was observed.

CASE II.—S. H., male, thirty years old, German. Admitted to Presbyterian Hospital. No history of alcoholism or of syphilitic infection. Excepting several attacks of malarial fever, general health good until two years ago, since which time there have been frequent attacks of nausea and vomiting, with severe headache and anorexia. For the few weeks prior to admission, great languor and muscular weakness with increasing gastric distress and vomiting were present. Patient vomited constantly for three days, and complained of fever and sore-throat.

Examination on admission. Anæmia decided, emaciation extreme. The entire surface of the body, and especially the skin over the chest, scrotum, and thighs, is of a dusky brown color. The hue presents a uniform gradation from that of a light mulatto on the chest to that of a dark negro in the above situations. No isolated patches of pigment, no icterus, conjunctivæ normal, no discoloration of the buccal mucous membrane. Acute catarrhal tonsillitis is present. The heart-sounds are feeble, and a pulmonic anæmic bruit is heard. The free border of the liver extends to the umbilical line. Spleen moderately enlarged. Urine contains albumin with hyaline and granular casts. Temperature 100°. Pulse 92.

The patient continued to vomit, the heart action failed, pulmonary œdema ensued, and delirium was succeeded by drowsiness, coma, and death. The urine was retained for twenty hours before death, and the final temperature reached 105°.

Autopsy. Heart-muscle soft, valves normal. Lungs normal. Liver enlarged, cirrhotic, mottled with hemorrhagic spots. Kidneys in condition of acute parenchymatous nephritis. Adrenals: both enlarged and completely degenerated, filled with caseous débris, no gland-structures remaining. Semilunar plexus and adjacent sympathetic nerves appear normal. Spleen double the normal size, dark, soft, pultaceous.

CASE III.—H. W., male, forty-four years old, Englishman, waiter. Admitted to the Presbyterian Hospital. Previous history of moderate drinking, attacks of malarial fever, rheumatism, and syphilis. Since having rheumatism, four years ago, the patient has had occasional œdema of the lower extremities and moderate dyspnœa upon exertion. Nine weeks previous to admission he began to suffer from anorexia, nausea, and vomiting, and lost strength and flesh. One week before admission he was seized with severe pain at the base and left side of the chest, which was followed by a chill the next day. He also complained of a painful dry cough.

Examination on admission. General nutrition good. Entire surface of body moderately pigmented; darkest on hands, face, and genitalia. Hue that of a light mulatto. No patches of pigment. No pigmentation of visible mucous membranes. Pulse very feeble, 100. No cardiac bruit. Temperature 101°. Dry pleurisy at base of left side of chest. Liver-dulness diminished in area. Splenic dulness increased. Urine normal.

On the third day effusion appeared in the left pleural sac, the heart action becoming extremely feeble, and uncontrollable nausea with vomiting and distressing singultus ensued. Both stomach and rectum rejected all food. On the eighth day a general convulsion and pulmonary œdema occurred, and the patient died in coma.

Autopsy. Besides the fluid in the left pleural sac, large lipomatous growths were found projecting from the pleural surface of the diaphragm on the left side, in masses resembling a cock's comb, which were 1½ to 2 inches long, and could be readily stripped off. Lungs œdematous, otherwise normal. Heart covered by a large layer of fat, valves normal, walls very soft. Liver small and slightly cirrhotic. Spleen enlarged by one-half and deeply pigmented. Kidneys surrounded by fat. They show early stage of chronic diffuse nephritis. Adrenals: each as large as a hen's egg, cortex completely caseous, medulla somewhat softer, but without pus. Not a trace of original structure remaining. Both surrounded by large accumulations of fat. No abnormality of semilunar ganglia observed.

CASE IV.—S. M. H., female, fifty-seven years old. Twenty months before her death, while in apparent good health, patient observed dark brown spots which first appeared on the neck, then on thighs and hands. Since then bronzing has become diffuse, and the patient has had occasional attacks of anorexia, nausea, vomiting, and prostration. She was twice admitted to the New York Hospital, with a year's interval. The first time that she entered the hospital her symptoms were mainly nausea, vomiting, epistaxis, insomnia, and muscular weakness, with moderate bronzing. After a few days the patient was discharged improved. Five weeks before admission for the second time, patient had severe vomiting, headache, constant pain in left hypochondrium, followed by rapid loss of flesh and strength. Has at times passed almost no urine, at other times has had moderate polyuria. Frequent epistaxis occurred.

On admission the integument was found deeply bronzed over the entire body, but especially so where exposed to the air. Conjunctivæ not pigmented, but lips and buccal mucous membrane spotted with dark gray patches. Anæmia was observed with marked asthenia, mental hebetude and despondency, and the pulse was weak, small and compressible. The patient died quite suddenly the same day of asthenia.

Autopsy. Body fairly nourished, rigor mortis well marked. Entire body distinctly bronzed with the exception of an old cicatrix one and a half inches in diameter in centre of forehead. Peritoneum, showing adhesions between liver and other viscera, and about the spleen. Heart brown, size normal, valves normal. Lungs, spleen, stomach, and intestines all normal. Liver small, cirrhotic, and pigmented. Brain and its membranes normal. Kidneys small, with adherent capsules and a few superficial cysts; cortex thin and markings indistinct. Adrenals: normal in size but irregular in thickness and nodular; cortex and medulla not distinguishable, studded with small caseous masses. Microscopic examination shows many small caseous areas surrounded by masses of young cells, with numerous giant-cells among them. No trace of original structure of medulla or cortex.

(The two following histories are incomplete in that they are without autopsies, but they illustrate the correlation of the symptoms of asthenia, pigmentation, vomiting, feeble pulse, etc.)

CASE V.—J. P., male, twenty-two years old, waiter, Englishman. Ill but two weeks with great muscular weakness with mental apathy. On admission to the New York Hospital the patient's condition was as follows: General nutrition good; no visceral lesion discoverable on physical examination, but the urine contains granular and hyaline casts. Blood examined and found normal. There was decided bronzing of a large surface of the body, especially over the chest and abdomen. The nipples were quite black. The patient appeared in a condition of melancholia, obeying when directed, but refusing to speak, and he would not voluntarily move or change his expression. Emaciation soon followed and became extreme.

After six weeks of treatment the mental condition failed to improve, and the patient was transferred to another institution.

(For the privilege of abstracting the two previous histories I am indebted to Dr. Peabody, in whose hospital service they occurred.)

CASE VI.—E. T., female, forty-six years old, laundress, Irish. History of occasional attacks of rheumatism and malarial fever. For sixteen months prior to admission to the New York Hospital, following exposure to cold and wet, the patient had occasional attacks of intense pain in the backs and hips, vertigo, headache, and severe vomiting. On admission, complained of shortness of breath, nausea, vomiting, and asthenia. Patient has noticed great variations in the quantity of urine at various times. Bowels constipated. For a year patient's skin has been growing uniformly dark, with brown spots on hands and body. Physical examination failed to reveal any visceral lesion. General nutrition good. Heart sounds very feeble, but without bruit; pulse 98, weak. Entire surface of body dark brown, inclining to black in certain regions. On the hands, feet, and body there were a few oval spots of darker hue than the surrounding skin. After some days of treatment the patient was discharged somewhat improved.

LESIONS OF THE ADRENALS.

Disease of the adrenals occurring as the sole lesion observed of any importance is recorded in nearly one-half of all cases, while in a further large number it accompanies, or is secondary to lesions elsewhere. But we are obliged to abandon the earlier theory that Addison's disease is etiologically dependent upon adrenal lesion, in view of the fact that many typical cases have lately been observed, such as one just cited (Case I.), with well-marked bronzing, in which the adrenal bodies were entirely normal. Among Lewin's histories 12 per cent. were of this type. Virchow describes a typical case with pigmentation, in which the microscopic examination of both the adrenals and sympathetic system presented nothing abnormal. Moreover, it is well established that every variety of adrenal lesion which has ever been found associated with Addison's disease has also occurred without giving rise to any symptoms whatever.

A most instructive case is related by Jürgens, where the pressure of a large aneurism caused atrophy and degeneration of the left splanchnic nerve with typical bronzing and other symptoms of Addison's disease, whereas the adrenals remained entirely normal.

In addition to the 40 cases of adrenal lesions which I have collected from hospital records, the existence of which gave rise to no symptoms of Addison's disease, are 72 others recently reported, making in all 112. Such cases must be common in the experience of anyone who is especially looking for them. The 40 unpublished notes are as follows:

CASES OF LESIONS OF THE ADRENALS ACCOMPANIED BY NO BRONZING OR ANY OTHER SYMPTOMS OF ADDISON'S DISEASE.

A. *Lesions other than simple fatty infiltration.*

CASE I.—Pleurisy, with effusion; hydro-peritoneum. Liver mottled and congested. Left kidney slightly enlarged, pale, with thickened cortex. Adrenals: normal in size, but cortex strongly pigmented (yellow).

CASE II.—Acute pleurisy, with effusion and ulcerative endocarditis. Liver infiltrated with fat; stomach mucous membrane dotted all over with a large number of petechial spots; kidneys showing diffuse nephritis. Adrenals: softened at centre, normal in size.

CASE III.—Cardiac valvular lesions and fibrinous pleurisy. Liver cirrhotic; capsule adherent to diaphragm. Kidneys: right waxy, left very large, filled with abscess cavity; left ureter obliterated and converted into dense connective tissues. Adrenals: both enlarged, with areas of yellow softening in medulla, cortex thickened and yellow in patches.

CASE IV.—Incarcerated hernia; gangrene of thigh. Adrenals: both enlarged and the seat of numerous hemorrhages and spots of softening.

CASE V.—Pernicious anæmia. Adrenals: both enlarged and cystic.

CASE VI.—Pulmonary embolism; large carcinoma of right supra-renal (left normal). No pigmentation of skin.

CASE VII.—Carcinoma of stomach. Hemorrhage in right supra-renal capsule.

CASE VIII.—Interstitial nephritis. Supra-renals much atrophied.

CASE IX.—Chronic diffuse nephritis. Adrenals: both cortices fatty. Interior of right completely degenerated.

CASE X.—Lobar pneumonia; chronic diffuse nephritis. Adrenals: both cortices fatty; right also cystic.

CASE XI.—Tubercular osteitis. Acute general miliary tuberculosis. Adrenals: both markedly increased in size, and containing many small grayish degenerated tubercular nodules.

For the notes of Cases IV. to XI. and for most of the cases of fatty adrenals cited below, I am indebted to Dr. Farquhar Ferguson, Pathologist to the New York Hospital, and to his assistant, Dr. George P. Biggs.

The reports of cases XII. to XXV. have been kindly given me by Dr. John S. Thacher, with whose permission I present the following notes: He says: "I have gone over the records of my autopsies at the Presbyterian Hospital, St. Luke's Hospital, and the State Emigrant Hospital. There are 971 of these in which the abdominal organs were examined. In most of them the condition of the adrenals was observed, and in the majority (575) it is found noted. In only 15 is it recorded as abnormal, certain variations in size, color, and consistence which are commonly met with not being classed as abnormal."

[One of these cases was genuine Addison's disease, and is referred to elsewhere; the remaining 14 are as follows:]

CASE XII.—April 12, 1889. Pulmonary tuberculosis, pneumothorax. Left adrenal contains a yellow nodule moderately firm. Right adrenal the same, but contains nodule three-quarter inch in diameter.

CASE XIII.—February 15, 1890. Tuberculosis of genito-urinary tract, lungs, intestines, cerebellum, cord, and adrenal. Left adrenal almost entirely replaced by a cheesy mass. Right adrenal normal.

CASE XIV.—July 13, 1890. Cancer of cardiac end of stomach; cancer of mesenteric and retro-peritoneal glands and liver; chylous ascites. Left adrenal contains white carcinomatous nodules.

CASE XV.—January 30, 1891. Fractured ribs; hemorrhage into pleura; acute pleurisy; hemorrhage into spleen; complete fracture of ulna. Left adrenal contains a nodule about one-third inch in diameter, rather soft in consistence, pinkish-yellow in color. Right adrenal contains a nodule like the other, but flattened, grayish in color, separating readily from the rest of the organ. Microscopic examination: cells fatty.

CASE XVI.—April 3, 1891. Chronic cystitis; chronic pyelo-nephritis. Right adrenal firm; on section found to contain a few pea-sized, firm, yellow masses. Left adrenal contains nodules like the right. Microscopic examination: typical tubercular inflammation.

CASE XVII.—February 8, 1892. Grippe; facial erysipelas; pneumonia. Left adrenal extremely thin, gray, of normal consistence; right adrenal the same. Microscopic examination: many leucocytes in spots; new connective tissue in some parts. The adrenal cells are some of them proliferated, some of them degenerated.

CASE XVIII.—April 2, 1892. Cancer of œsophagus; gangrene of lungs; gastrotomy. Left adrenal contains a nodule one-half inch in diameter. Right adrenal contains a similar nodule one inch in diameter. Microscopic examination: carcinoma, typical.

CASE XIX.—May 5, 1892. Chronic pulmonary phthisis. Left adrenal normal, except a pea-sized, yellow, caseous nodule.

CASE XX.—September 2, 1891. Tubercular ulcers of intestines; perforatiom; peritonitis. Left adrenal, one end enlarged; on section shows a grayish, moderately firm mass three-quarters inch in diameter. Right adrenal the same. Microscopic examination: section consists almost wholly of small cells, little larger than leucocytes, mostly not round, but pea-shaped and irregular, no alveoli; looks like sarcoma.

CASE XXI.—January 25, 1893. Chronic tuberculosis of hip-joint; waxy degeneration of liver, spleen, and kidneys; broncho-pneumonia; acute pleurisy. Left adrenal appears normal. Microscopic examination: typical tuberculosis.

CASE XXII.—October, 1889. Cancer of lungs, heart, liver, kidneys, and adrenals. Latter contain small nodules one-quarter inch in diameter.

CASE XXIII.—February 17, 1892. Paris-green poisoning; acute gastro-enteritis. Right adrenal contains a yellowish nodule about one-half inch in diameter, a little softer than the rest of the organ. Left adrenal normal. Microscopic examination: mass of adrenal cells in rather irregular alveoli, most of them in a state of marked fatty degeneration; a little infiltration of leucocytes at the periphery.

CASE XXIV.—March 26, 1892. Chronic nephritis; cirrhosis of liver; cardiac hypertrophy and dilatation. Right adrenal is replaced by a mass about twice the size of the normal organ, gray and granular. Left adrenal normal. Microscopic examination: typical tubercular inflammation.

CASE XXV.—April 21, 1893. Chronic cystitis; abscess of seminal vesicle; external urethrotomy; pyelo-nephritis; miliary tuberculosis of lungs. Both adrenals contain cheesy nodules. Microscopic examination: cheesy spots surrounded by infiltration of small cells and epithelioid cells; probably tubercular.

"I recall also two cases of diseased adrenal, not contained in the records mentioned. One was an employé at the State Emigrant Hospital, who slowly and gradually became anæmic and asthenic, but no cause could be detected. His color was very white. After autopsy the adrenals were found cheesy.

"The other was a patient in the Colored Hospital. I can only recollect that at the autopsy the adrenals were cheesy and the tongue showed brown patches, and it was concluded that he had died from Addison's disease." (Thacher.)

The following case (XXVI.), as well as Case XL., was kindly examined for me by Dr. Warren Coleman, Instructor in Pathology, Loomis Laboratory, New York:

CASE XXVI.—Catarrhal pneumonia; cheesy foci in lungs; cardiac hypertrophy and dilatation; kidneys hard, congested, surface rough, cortex diminished. Adrenals: right normal; lower portion of left degenerated and converted into a white homogeneous substance. Microscopic examination shows the cells not filled with fat but with scanty protoplasm, leaving the nuclei intact in the centre of a reticulum. No necrotic areas; no congestion. Only a few normal cells are found, chiefly in the zona glomerulosa.

Semilunar ganglia (of both sides): The nerve-cells are distributed unequally throughout the ganglia. In many instances a definite sheath can be made out around them. Nerve bundles run through the ganglia at different points. Between the cells there is connective tissue with long oval nuclei resembling the nuclei of involuntary muscle. The tissue is most abundant where the cells are fewest. The nuclei are normal in shape. Nucleoli prominent. Many of the cells are pigmented with small golden-brown granules scattered through the protoplasm. They resemble hematoidin granules.

B. *Fatty changes.*

CASE XXVII.—Cirrhosis of liver. Adrenals both contain considerable fat in the cortices, more abundant in the left than in the right.

CASE XXVIII.—Croupous pneumonia. Adrenals both very fatty.

CASE XXIX.—Lobar pneumonia. Adrenals both contain fat in the cortices.

Case XXX.—Cirrhosis of liver; pulmonary tuberculosis; chronic diffuse nephritis. Adrenals both contain much fat in the cortices.

Case XXXI.—Lobar pneumonia. Right supra-renal body normal. Left contains much fat.

Case XXXII.—Ulcerative endocarditis; aortic insufficiency. Adrenals: both cortices fatty.

Case XXXIII.—Lobar pneumonia. Adrenals: both cortices fatty.

Case XXXIV.—Lobar pneumonia (bilateral). Adrenals both contain considerable fat.

Case XXXV.—Aneurism of thoracic aorta; pneumonia; chronic diffuse nephritis. Adrenals both very fatty, the fat irregularly distributed throughout the cortex in patches of various sizes.

Case XXXVI.—Chronic diffuse nephritis; entero-colitis. Adrenals both very fatty.

Case XXXVII.—Myocarditis; diffuse parenchymatous nephritis. Adrenals both contain a great deal of fat diffused throughout their entire cortices.

Case XXXVIII.—Aneurism of thoracic aorta; lobar pneumonia. Adrenals both very thick, and contain much fat in cortices.

Case XXXIX.—Pyo-pneumothorax; pulmonary tuberculosis. Adrenals both very fatty.

Case XL.—Dilatation of aorta; cardiac hypertrophy; miliary tubercles in lungs; kidneys small, capsule adherent, markings indistinct. Adrenals—microscopic examination: majority of cells in zona fasciculata contain small fat globules of various sizes, or one large globule displacing the nucleus. Some of these cells are distended. Other cells have lost their nuclei and are granular and necrotic. Portion of medulla next to cortex normal, except for congestion, which is evident throughout the section.

The entire list of 112 cases, without symptoms of Addison's disease, includes: Extensive pigmentation; cloudy swelling from cases of infection from pathogenic organisms (*Brit. Med. Journ.*, May, 1889); atrophy, infiltration with small, round cells; fatty infiltration; tubercular inflammation (with bacilli); several simple cysts; two cases of hemorrhagic cyst; one of gumma; and a number of adenoma, sarcoma, and carcinoma.

Twice the supra-renal bodies have both been congenitally absent (Martini, *Comptes rendus*, 1856, xliii. p. 1053; Spender, *Brit. Med. Journ.*, September 11, 1858); and four times either the right or left has existed alone. Dr. Hartley recently told me that he has removed a supra-renal capsule in connection with excision of the kidney without the subsequent occurrence of any noteworthy symptoms.

In view of the opposing facts, the immediate causative relation of supra-renal lesions to the symptoms of Addison's disease cannot be easily maintained, in spite of their frequent coincidence, and we must seek a further explanation in the relation between the adrenals and the sympathetic nervous system. To this subject it will be convenient to return.

ADRENAL TUBERCULOSIS.

Two facts must be admitted regarding adrenal tuberculosis:

First. The supra-renal bodies are far more susceptible to tubercular inflammation than to any other form of disease.

Second. Addison's disease occurs oftener in conjunction with tuberculosis than with all other diseases together, or in approximately 80 per cent. of all cases. Hence, when tuberculosis invades the adrenals Addison's disease usually develops, although other and more important factors may be concerned in the process.

We find all the later stages of tubercular inflammation and of tubercular deposits in the adrenals, but their exact nature and extent have never been shown to bear any definite relation to the accompanying symptoms. Tubercle bacilli have been reported as present in the adrenals in a score of cases, but more often they are not found. In three recent instances the adrenals have given very marked reaction to inoculation with Koch's tuberculin, and in one of these there was extensive hemorrhage into the degenerated supra-renal body. In the great majority of cases both adrenals are involved; when the tubercular process is present in but one, the left is affected twice as often as the right.

The local tuberculosis frequently commences as a primary chronic inflammation, interstitial, and accompanied by the formation of small tubercles, which enlarge, coalesce, and degenerate to caseous masses that may soften and honeycomb the entire adrenal structure with cavities which are often described as containing pus, though the material is usually simple granular débris with oil globules. This substance may be replaced by calcareous matter, and sometimes, but less often, atrophy ensues. The inflammatory process commonly begins in the medulla and extends to the cortex, gradually obliterating all original structure, but the reverse may be the case, or both may be simultaneously affected. Adhesions and thickened masses of connective tissue, or deposits of fat, are very apt to form about the adrenal bodies, and it is important to note that such changes often involve or include the adjacent sympathetic nerve and ganglia.

THE RELATION OF ADDISON'S DISEASE TO OTHER DISEASES THAN TUBERCULOSIS.

This subject deserves brief mention.

Malarial Fever.—The accompanying anæmia in Addison's disease, and the fact that the spleen has certain physiological influences in regard to the chief pigment of the body, suggests the question whether malarial fever is associated in any special manner with the former affection. In the cases which I have personally seen there had been many attacks of malarial fever. Other observers have commented upon a similar coincidence. Lewin reports forty-five cases. But it has not been shown that Addison's disease is more frequent in those regions where malaria is most severe, nor does it bear any constant relation to malarial paroxysms when the two diseases coincide. The spleen is sometimes hyperæmic and is pigmented in Addison's disease, but it is frequently normal, and our present knowledge does not enable us to recognize an etiological relation between the two affections.

Carcinoma.—With regard to carcinoma of the adrenals, whether it involves them primarily, as it has been rarely known to do, or by extension from contiguous organs, it is a remarkable fact that, as a rule, this lesion does not provoke either pigmentation of the skin, or typical symptoms of Addison's disease. Such a result has only once or twice been recorded (Fleiner, *Berl. klin. Wochenschr.*, December 23, 1889). The same may be said of sarcoma and adenoma.

Caries.—Several cases of vertebral caries have occurred in conjunction with symptoms of Addison's disease, in which the local sympathetic system was also more or less involved.

Goitre.—Three cases of coincident exophthalmic goitre have been observed. This fact is of special interest from the possibility of a connection having existed between abdominal and cervical sympathetic nerve lesion or irritation.

In general, it must be admitted that no other disease than tuberculosis accompanies Addison's disease with sufficient frequency to be regarded as among predisposing causes.

Traumatism, or strain affecting especially the muscles of the back, has been reported several times as the exciting cause of Addison's disease in cases in which tuberculosis could be excluded.

In one instance the disease followed immediately upon a severe wrench of the back acquired while skating, and in another a fall into ice-cold water. Several cases have developed in connection with psoas and lumbar abscess from injuries of the spine.

AGE.—Addison's disease was originally held to belong only to adult life. Lately, however, two cases have occurred in infants only seven days old, and in one eight days old. All showed distinct bronzing. In one infant one adrenal was cystic and not caseous. Girode (*Bull. de Soc. Anat.*, April, 1891) reports the history of a newborn infant who had syphilitic adrenal gummata, without bronzing. Addison's disease has been observed in almost every year of life from birth to the eighty-first.

SEX.—Sixty per cent. of all cases occur in males.

DURATION.—While the average duration of all cases is from two or three months to a year, there are remarkable exceptions. One patient has lived ten years and another nearly eleven years (Schreiber, *Berl. klin. Wochenschr.*, October 13, 1890; Schmaltz, *Deutsche med. Wochenschr.*, September 4, 1890). A number of others are reported as living respectively four, five, seven, and eight years after pigmentation was first observed.

It is difficult to account for the prolongation of life in a few cases of a disease which is otherwise so uniformly fatal at an early date.

SYMPTOMS. *Pigmentation.*—The belief that adrenal lesions are responsible in any direct manner for the bronzing of the skin, and sometimes the mucous membrane, is not sustained by analysis of reported autopsies. The theory has been advanced that the adrenals were more glandular structures than nerve organs (Virchow), and that the bronzing is due to a glandular chromogenic action of the supra-renal bodies. In other words, first, that they either alter normal hæmoglobin, constantly passing through their abundant bloodvessels, and return it to the blood; or, second, that they form new pigment when diseased; or, third, that, becoming diseased, a certain controlling influence ordinarily exerted over the blood pigment is removed. Many facts derived from a careful study of the embryology, physiology, and pathology of the adrenals are arrayed against these views.

The adrenals have long been known to furnish peculiar color reactions (Vulpian et Baunie, *Gaz. hebd. des Sci. Méd. de Bordeaux*, 1888, No. 11). They become reddened by oxidation in light and air, are blackened by per-salts of iron, and turned green by dilute iodine solutions. Klebs has claimed that following irritation a chromogenic body is stored in the adrenal cortex in increased amount.

I have repeated the color test with the adrenals of man and nearly all the domestic animals, and have never found them to fail. The deep green produced by brushing the freshly cut surface with sesqui-chloride of iron affects the medulla and not the cortex. This reaction is unique. Notwithstanding the peculiar color reactions, there is no conclusive evidence that the pigmentation of Addison's disease depends upon alterations in the blood; for the bronzing is often great while the blood is normal and no excessive pigment has been found in it, neither is the urinary pigment increased. The only remaining hypothesis is that there is some peripheral sympathetic influence at work which causes the deeper cells of the rete Malpighii to appropriate and alter the blood pigment which circulates in the capillaries among them. This pigment is found in the protoplasm of the younger cells in the situation where it is normally present in the negro in excess (Sjostrom, *Deutsche med. Wochenschr.*, May 30, 1889). Jürgens (*Deutsche med. Zeitung*, May 10, 1888), believes that some pigmentary substances may be deposited through peripheral nerve excitation, originating in epithelial degeneration or external irritation, hence the pigmentation is most decided where the skin is exposed, in the face and hands, on flexures and folds, etc.

Gade (*Fortschritte der Med.*, 1889, No. 12, p. 452), who has found pigmentary deposits in large branching cells in the velum palati and tongue, as well as in other mucous membranes and the skin, believes that the bronzing of Addison's disease is not the result of any specific action, but is merely an increase in the normal amount of pigment locally deposited from the hæmoglobin.

The fact has been confirmed by many observers (Lancereaux, Nothnagel, Fleiner, *et al.*), that the pigmentation occurs most prominently in those cases in which the sympathetic nerves are found diseased. I have been told by Dr. C. S. Bull that he has examined the eyes of a number of patients with Addison's disease, but never found increase of pigment in the fundus oculi, though in one case it was present in excess in the iris.

I have referred to 112 cases of adrenal lesion in which no bronzing appeared at any time. These abnormalities were of great variety, covering the range of pathological changes from simple hyperæmia to advanced caseation or calcification of the entire adrenal structure, yet at no period were the integument or mucous membranes pigmented in the slightest degree.

If the pigmentation of the surface depended upon functional derangement merely of the adrenals, by abolishing a control over the normal blood pigment, surely it could not be absent throughout widespread progressive destruction of their tissue. On the other hand, it cannot be alone due to new pigment formed by the supra-renal bodies, for fully twelve per cent. of all cases of typical Addison's disease have been unaccompanied by any adrenal lesion whatever.

Chemical analyses (Thompson and Costello) of the supra-renal bodies, in addition to the excess of pigment above described, shows that they contain leucin and myelin in quantities out of proportion to the number of nerves, also traces of hippur taurocholic, and benzoic acids, but nothing which is peculiar to the adrenals, or which is not found in other situations in the body in greater amount.

OTHER SYMPTOMS AND VISCERAL LESIONS IN RELATION TO ETIOLOGY.

Careful analysis of the symptoms recorded in all cases of Addison's disease shows considerable uniformity in the occurrence of functional or other disorders of the alimentary canal and of the circulation, and suggests very forcibly the probable existence of a common cause to be found in disturbance of the abdominal sympathetic system.

Vomiting.—In almost every case nausea and vomiting are present, and with asthenia they are often the first symptoms observed. The vomiting, at first paroxysmal, occurring at very irregular intervals, becomes more and more frequent and severe. It is not referable to errors in diet, nor to gastric lesions. In a few instances slight gastritis or hyperæmia or pigmentation of the mucous membrane of the stomach have been noted, but these conditions are neither frequent nor prominent enough to account for the severe emesis.

It has been suggested that this symptom is due to an altered condition of the blood, or to the presence of some toxin generated by the suprarenal bodies. But the vomiting may occur long before there has been time for alterations in the composition of the blood to appear, and the latter are usually neither frequent nor serious. It seems more probable that the emesis is due to an irritation of the cœliac plexus, which reaches the vomiting and respiratory centres through branches of the vagus nerve. We have many proofs of the possibility of this occurrence, and a functional irritation of the sympathetic nerves even without destructive lesion may be a sufficient factor, as in the vomiting of pregnancy, forms of severe abdominal pain like that accompanying the passage of gall-stones, or renal calculi, certain ovarian diseases, etc.

Diarrhœa.—The same argument may be employed to account for the diarrhœa which is so commonly present. This is found to be more than twice as frequent as constipation, which as a rule occurs only at the commencement, and as in the case of vomiting, it does not bear any definite relation to errors in diet, nor is it excited by other common influences, such as exposure to changes in temperature, intestinal hyperæmia, etc. Lesions of the intestine, excepting occasional hyperæmia and ecchymosis, and cases where general tuberculosis with ulceration exists, are so rare as to be regarded merely as coincidences. On the other hand, there is much experimental evidence in favor of the belief that diarrhœa, like emesis, is produced in this disease by splanchnic irritation rather than by altered blood or any other agency.

Lewin and Israel have shown that removal of the cœliac ganglion produces at first constipation and later diarrhœa, and the musculo-motor and vasomotor impulses which emanate from it may be so modified by expermental irritation as to alter peristalsis, or produce local anæmia or hyperæmia. These results have been confirmed by others. In animals extirpation of the solar plexus gives rise to hyperæmia, ecchymoses and ulceration in the wall of the stomach and upper portion of the small intestine.

In a few instances atrophy or swelling and pigmentation of the solitary and Brünner's glands and Peyer's patches have been recorded, and this may be explained by the influence of the cœliac plexus through altered trophic impulses. That these lesions are not more frequent may be due to the fact that the trophic influence is not very strong, or it is modified by the local plexuses in the intestinal wall.

Nothnagel has shown a relation to exist between atrophy of the intestinal wall and atrophy of the intestinal sympathetic plexus, although the splanchnic nerves were intact.

Changes in the other abdominal viscera are neither frequent nor extensive, and consist mainly of hyperæmia, which might also be due to sympathetic irritation or lesions.

The spleen has been found hypertrophic and often soft and pigmented, but it has been pointed out that the occurrence of coincident malarial fever with Addison's disease is not unusual.

The liver may be hyperæmic, cirrhotic, tubercular, or, as in one of my cases, syphilitic. There is nothing characteristic of Addison's disease in its various lesions. The mesenteric glands are frequently enlarged and caseous, but this is mainly in distinctly tubercular cases.

The kidneys and urine are usually normal, and mellituria has not been observed. Hyperæmia and moderate hypertrophy of the kidneys are reported in a few instances. This is also possibly due to blood stasis or altered blood-pressure produced through splanchnic irritation.

Pain and Tenderness.—In fully one-third of the cases, sharp neuralgic, or more often severe dull aching pains are present, and referred principally to the lumbar region, but also to the deep epigastric and hypochondriac region. The pain in most cases has been accompanied by extreme local soreness and tenderness on pressure (Henry, *Trans. Path. Soc. Phila.*, vols. v., x). Müller (*Handb. der Physiol.*, i. p. 579), and Höffter (*Henle u. Pfeuffer's Zeit.*, N. F., iv. S. 322), have demonstrated that experimental irritation of the cœliac ganglion gives evidence of acute sensibility; and severe colic may, of course, occur independently of serous or intestinal muscular lesions. It seems, then, probable that the lumbar and abdominal pains of Addison's disease may emanate from splanchnic irritation.

The Lungs.—In about two-thirds of the cases the lungs or bronchial glands have been affected in various ways. The majority of cases are tubercular. In other instances hyperæmia, œdema, and pigmentation are recorded with pleuritic adhesions. Caseation and hypertrophy of the bronchial glands have been reported. The frequent occurrence of tubercular degeneration of the adrenals is thus explained in many instances as a secondary involvement, following the primary infection of intra-thoracic tissues.

The Pulse.—The modifications in the circulatory system are mainly referable to the pulse, which is uniformly small, compressible, and feeble, and usually rapid in the latter stages of the disease. Heart lesions are infrequent and the valves are usually normal. Atrophy of the heart has been observed twenty-seven times, and hypertrophy, brown pigmentation and fatty degeneration have occasionally been found. These conditions are too infrequent to account for the enfeeblement of the pulse, and since the latter may be present in acute cases when the blood appears normal, and before the general nutrition of the patient is seriously impaired, it is highly probable that it is due to functional or reflex disturbances of the circulation coming from the abdominal sympathetic system.

When the vasomotor tone in the splanchnic system is lowered by experimental irritation, the general arterial pressure is reduced, producing cerebral anæmia and lessening the vagus tone. As a further result, the pulse becomes quick, small, and compressible. The theory is advanced by Henry and others that paralytic distention of the abdominal blood-vessels is produced through functional or organic causes by their acting upon the sympathetic system, disturbing the equilibrium of the circulation.

The central nervous system exhibits no typical lesions. Cerebral anæmia and hyperæmia are both recorded in about a dozen cases. Vertigo is frequently observed, and there is often mental weakness and depression, with loss of energy. In protracted cases delirium and coma result, and in a few convulsions have been present. It is not uncommon for death to occur very suddenly through a condition resembling shock, or as it sometimes follows severe blows upon the abdomen. Patients are very apt to show more or less lethargy and mental dulness.

The asthenia, which is usually pronounced, appears so early that there is no muscular atrophy and no loss of adipose tissue, and it is difficult to believe that it is not due to nervous influences rather than to changes in the blood, or malnutrition. Dyspnœa may accompany this condition.

The Blood.—Anæmia is common but by no means extreme, and careful clinical study of the blood fails to establish satisfactorily the theory that the disease is essentially a blood disease. Free pigment is not found. While the red corpuscles may be diminished in number they do not appear otherwise abnormal, and in certain typical cases anæmia has not been present. In some of the more acute cases the symptoms become well marked before the general nutrition has been appreciably impaired. The hypothesis that the symptoms are due to a toxin developed by the adrenals and discharged into the blood is not supported by evidence of value, and many facts are directly opposed to it. Ecker first described the adrenals as blood glands, in 1846, before Addison's disease was thought of, and recent inoculation experiments with the thyroid and various gland substances, and the general belief that the chemical composition of the blood is normally influenced by many different organs of the body, tempt one to regard the adrenals as possibly possessing a similar control, but the experiments upon animals, which I will presently report, fail to support this theory.

Rare symptoms have occasionally been observed complicating the usual type of Addison's disease, and they are of interest only in connection with the possibility of origin through extreme irritation of the sympathetic nerves. One instance of salivation is reported, one of bromidrosis, and one of nutritive disturbance in the mammæ, uterus, and other female generative organs. The mammæ and ovaries were greatly atrophied (Kleinwachter, *Lancet*, January 25, 1891). The disease has once been observed in a "bleeder." (Schmaltz, *Deutsche med. Wochenschr.*, September 4, 1890.)

The group of symptoms above considered—namely, the nausea; irritable paroxysmal vomiting and diarrhœa; localized lumbar and epigastric pain; enfeebled pulse; mental apathy and prostration; and the hyperæmia—all point toward a common origin in a lesion which excites or irritates the abdominal sympathetic system, and not necessarily the semilunar ganglion alone, but at times the stomachic, hepatic, or mesenteric plexuses.

EXPERIMENTS UPON ANIMALS.

For the past four months I have been experimenting at the Loomis Laboratory upon the supra-renal capsules of various animals.

Without entering too much into details in this paper, I will briefly state the results: The experiments were performed upon the cat, dog, rat, guinea-pig, and rabbit, and consisted of transplantation, excision, and destruction of the adrenals, and inoculations of aqueous and glycerin extracts made from the adrenals of these animals, and from man in a case in which the capsules were obtained from an autopsy six hours after death from chronic cardiac disease.

Transplantation was performed by inserting the freshly excised adrenals from an animal of one species in the abdominal wall or abdominal cavity of another. After a few days or a week the adrenals were found degenerated, softened, and apparently undergoing absorption.

Excision of the adrenals is one of the most difficult operations which I have ever undertaken upon animals, especially in the dog. They are so deeply situated that they are difficult to reach from behind, on account of the thickness of the muscles of the back, and if approached from the front or side, so much displacement of overlying organs is necessary that irritation or injury of adjacent nerves is unavoidable. Moreover, in all the animals used, a very large vein from the abdominal muscles lies directly across the ventral surface of the adrenals in a groove which divides them into two lobes connected with a narrow isthmus. This vein is joined by a relatively large branch from each supra-renal body. The latter usually lies on the right side in direct contact with the vena cava, and on the left with the renal vein. It is therefore almost impossible to ligate the muscle vein, and of course hemorrhage from such a large branch of the vena cava or renal vein is soon fatal. To obviate this occurrence I have destroyed the adrenal bodies by the actual cautery. Animals thus treated make a good recovery and exhibit no symptoms. There is no increase in pigment of the mucous membrane or elsewhere, the blood is normal and digestion is good. A similar lack of symptoms is observed after transplantation of the glands.

A curious fact in relation to the adrenals has been observed by Stilling (*Virch. Arch.*, December, 1889), namely, that in a young animal after extirpation of one of these bodies the other hypertropies to a considerable extent. The result would seem to indicate that the organ is not a mere relic of the embryonic state, but is of some functional value.

Ablation of both adrenals is reported by many observers to cause death within a period varying from a few days to several weeks, and Tizzoni claims to have found resultant lesions of the nature of alterations in the walls of bloodvessels, hemorrhages, extravasations, and disturbances of the lymphatic circulation. He also claims to have observed in connection with the brain and cord, infiltration with leucocytes and fibrinous exudation, but these results have not been corroborated by any of the numerous experiments made by others when careful antisepsis is maintained.

Arnaud, Marino-Zucco and Guarnieri have extracted substances from fresh supra-renal bodies which they describe as acting as toxins. After using rigid antiseptic precautions they found that injection, even in small doses, of these materials subcutaneously or into the veins of dogs, rabbits, and guinea-pigs, produces death in a short time.

One substance isolated by them is described as a phospho-glycerate of neurin. I have made a number of inoculation experiments upon animals with glycerin and aqueous extracts prepared from the freshly excised adrenals, and am convinced that if proper antiseptic precautions are employed, the supra-renal bodies possess no toxicity when ingrafted or inoculated in animals.

An extract of both adrenals from a dog injected into another dog or into a cat or rabbit, seems entirely without effect. In some cases I repeated the inoculations with the extracts several times in the same animal, which was kept alive for two months without symptoms.

Jaboulay (*Lyons Méd.*, November 2, 1891), has described the occurrence of accessory supra-renal bodies situated upon the semilunar ganglion and in the midst of the solar plexus. I have several times observed these supernumerary bodies, and they have been reported as occasionally present in man.

Lesions of the Sympathetic System.—It is greatly to be regretted that thorough microscopic examination of the abdominal sympathetic nerves and ganglia has not been more frequently made in the reported cases of Addison's disease, for there is good reason to believe that lesions can be very often found in these structures. The earlier records are practically valueless in this regard, for they were made at a period when the technique of nerve preparation and staining was very imperfect as compared with present methods, and slight lesions even if sought for might easily have escaped observation.

The research of the past four or five years, however, is constantly bringing to light an increasing proportion of cases of Addison's disease in which the condition of the various sympathetic nerve structures is shown to be abnormal. The ganglia are often excessively pigmented, sometimes hemorrhagic. They may exhibit fatty degeneration, swelling, and even caseation and suppuration. Their nerve-cells are atrophied, the vessel walls are thickened and infiltrated, the nerves have a thickened perineurium, and there may be degeneration of the axis cylinders. Such degenerative changes have been lately observed in the splanchnic, in the semilunar and solar ganglia, and in the plexus surrounding the abdominal aorta. Fleiner (*Berl. klin. Wochenschr.*, No. 22, 1891), gives an account of two typical cases in which signs of inflammation were present in the ischiatic, crural, median, and vagus nerves. In one case there was a neuritis of the lower posterior spinal nerve roots, and some degeneration of the posterior columns of the cord. (Kalindero and v. Bates, quoted in *Schmidt's Jahrb.*, No. 1, 1893.) Such cases may be coincident with adrenal degeneration or occur without it; not infrequently the diseased adrenals are adherent to surrounding organs, and various sympathetic nerve branches are included in the proliferated connective tissue.

Armand and Alezais (*Semaine Méd.*, October 7, 1891; *Marseilles Méd.*, January 30, February 28, March 30, 1892) have examined microscopically the lesions of a large number of cases, and they failed to discover nerve-cells in the medulla of the supra-renal bodies, but upon their periphery, especially at the posterior surface, are "peri-capsular ganglia," which they declare are always implicated in Addison's disease, even when the semilunar ganglion and sympathetic nerves are not. On the other hand, Lewin (*Charité Annalen*, vol. x. p. 722) describes many axis cylinders in connection with ganglion cells in the adrenals.

I have been able to find only 81 published histories in which positive mention is made of the sympathetic system, and four of these may be regarded as incomplete, because no note is made of microscopic examination. Of the remaining 77 cases, 60 presented decided lesions of the sympathetic nerves or ganglia. Among the 30 cases most recently examined 27 had such lesions. This is certainly a very striking fact, taken in connection with the analysis of the symptoms of Addison's disease above given, in which I have attempted to show the possibility of the direct cause being an irritation proceeding from the abdominal sympathetic system. Are we not in a position to adopt the following

CONCLUSIONS.

First. That Addison's disease is a condition arising from and dependent upon irritation of the abdominal sympathetic nerves through lesions of themselves, their ganglia, or diseased supra-renal capsules.

Second. In the great majority of instances (fully 80 per cent.) the disease originates as a secondary or primary tuberculosis in the adrenals, and the sympathetic system is either involved by extension of pathological processes, or is functionally disturbed and irritated through the intimate anatomical connection existing between the adrenals and the relatively large number of nerves which they contain.

Third. Actual lesion of the sympathetic system, while far more common than heretofore supposed, is not necessary to produce the varied symptomatic phenomena of the disease. Functional disorder, through irritation conveyed from the adrenals, may sometimes cause all the symptoms—just as in chorea and in many of the conditions of aggravated hysteria, and other functional nervous disorders, we are often unable to find definite lesions.

Fourth. In a certain proportion of cases (not over 20 per cent.) the adrenals are affected by some other lesions than those of tuberculosis, or else they remain normal (in 12 per cent.) and the sympathetic nerves and ganglia are alone diseased.

I am aware that the objection may be raised that excessive pigmentation and even more extensive alterations are not infrequently found in the sympathetic ganglia, giving rise to no symptoms whatever (as in Case XXVI. above reported), and also that there is a tendency of late among physiologists to assign less independence and less functional importance to the sympathetic nerve system. In Addison's disease there are but three reasonable hypotheses to account for the symptoms, namely, that it is a blood disease; that it is due to adrenal toxins; or, that it is due to sympathetic irritation, either functional or organic. The latter hypothesis, while perhaps not wholly satisfactory, appears to be supported by much weightier evidence than either of the others.

While these views are not new (*vide* Greenhow "On Addison's Disease," Croonian Lectures for 1875), by many they have not been finally adopted, because experimental and statistical data have been very slowly accumulated; and it has been my aim, by experiment and by analysis of all recorded cases, to place on a somewhat firmer basis the belief that Addison's disease is dependent upon lesion or irritation of the abdominal sympathetic nervous system.

THE BACILLUS PYOCYANEUS PERICARDITIDIS.[1]

By Harold C. Ernst, A.M., M.D.,
ASSISTANT PROFESSOR OF BACTERIOLOGY IN HARVARD UNIVERSITY; PHYSICIAN TO OUT-PATIENTS AT THE MASSACHUSETTS GENERAL HOSPITAL.

Much attention has been given of late years to the effects of the cultures, and their products, of Gessard's B. pyocyaneus, especially in anthrax. At various times authors have announced the isolation of bacteria very closely resembling this, but the only one that seems to have gained a permanent place in literature is the B. pyocyaneus β of

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[1] Presented at the annual meeting of the Association of American Physicians, May, 1893.